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PHYSICAL PERFORMANCE CAPACITY OF RATS DURING BACTERIAL INFECTIO--ETC(U)
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A usable model for evaluating alterations in performance capacity during bacterial infections is described in which two strains of laboratory rats were inoculated with varying doses of Streptococcus pneumoniae and Francisella tularensis and forced to swim. Rat strain differences played an important role in the animals' response to infection and exercise. Variability between individual naive rats was encountered and a 60-min swim test (1 week prior to inoculation) was used to standardize work performance. Swimming capacity was

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reduced by either disease, their effects increasing with time postinoculation. Prior experience with the swim task altered disease-induced decrements, but did not change the animals' response to a lethal challenge of either microorganism. Time of exercise in relation to disease exposure was also important. Strenuous exercise postinoculation increased disease-related mortality, while a swim immediately before inoculation reduced susceptibility to lethal doses of either bacteria. Daily exercise was found to evoke a training respone by limiting the infection-induced decrement in performance capacity.

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Running head: SWIMMING DURING INFECTIONS

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council. The facilities are fully accredited by the American Association for Accreditation of Laboratory Animal Care.

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Abstract

A usable model for evaluating alterations in performance capacity during bacterial infections is described in which two strains of laboratory rats were inoculated with varying doses of *Streptococcus pneumoniae* or *Francisella tularensis* and forced to swim. Rat strain differences played an important role in the animals' response to infection and exercise. Variability between individual naive rats was encountered and a 60-min swim test (1 week prior to inoculation) was used to standardize work performance. Swimming capacity was reduced by either disease, their effects increasing with time postinoculation. Prior experience with the swim task altered disease-induced decrements, but did not change the animals' response to a lethal challenge of either microorganism. Time of exercise in relation to disease exposure was also important. Strenous exercise postinoculation increased disease-related mortality, while a swim immediately before inoculation reduced susceptibility to either of the bacteria. Daily exercise was found to evoke a training response by limiting the infection-induced decrement in performance capacity.

Key words: swimming; exercise; performance capacity; infection; rat; bacteria; experience.

SWIMMING EXERCISE has been extensively utilized to evaluate the influence of various environmental and nutritional conditions on work capacity (3), but very little is known regarding the interactions of exercise and bacterial infections. Previous human studies indicated a loss or impairment of performance capacity in cardiovascular response to disease in general (23). Recently, Friman and Ilbäck (6) demonstrated a detrimental effect of swimming during Francisella tularensis infection in rats. However, dose response and performance decrement relationships were not clarified.

Studies were performed to ascertain the influence of exercise on infected rats. The studies correlated work reduction to disease intensity, duration of illness and time of inoculation in reference to time of exercise, and the altered mortality incidence of varying inocula of two bacterial infections in different strains of laboratory rats. Streptococcus pneumoniae infection was chosen as a model gram-positive bacterium whose pathogenesis has been described (15, 16). F. tularensis was chosen as a model facultative intracellular gram-negative bacterium with known pathogenicity (4, 14). Inocula were varied to produce a systemic disease in which rats became moribund and began to die at 18 h at the higher doses of each organism.

Definitions. In these studies, experience is defined as the learned response after completion of a 60-min swim test. Performance in this study refers to swimming for different time periods, while performance capacity is the maximum ability to swim as measured by time to exhaustion. Training occurs as a result of repeated sessions of exercise with stepwise increases in duration of swimming and improved efficiency.

MATERIALS AND METHODS

Animals. The animals utilized in these studies were male Fisher-Dunning rats (F-344/Mai f, MA BioProducts) and male Sprague-Dawley rats (Tac:N [SD] fbr, Taconic Farms, Inc.) weighing 175-200 g. Rats were maintained on a commercial diet until the beginning of the experiments. Five rats were housed per cage in rooms maintained on a 0600-1800 hours light cycle at 23 $\pm$ 1°C temperature; water was supplied ad libitum. All rats were acclimated for at least 7 days prior to the day of experimentation.

Infections. Rats were inoculated subcutaneously (s.c.) in the groin pouch with virulent *S. pneumoniae* Ia5 or intraperitoneally (i.p.) with *F. tularensis* live vaccine strain (LVS), at the doses per 100 g body weight, shown in the legends of figures 1 and 2. Controls received an equal number of heat-killed bacteria. Rats were fed ad libitum up to time of infection. On day 0 of each experiment, all food was removed from both heat-killed and infected groups to more closely resemble the infected animals, which become anorectic. Fed rats served as additional controls. The responses to the disease were characterized by a rise in rectal temperature and a depression of plasma zinc (data not shown), as described by Neufeld et al. (15). All exercised-infected animals were febrile when forced to swim.

Swimming exercise. Rats swam in 32-gal steel barrels with a 50-cm diameter filled with tap water. Rats were exercised in groups of five to insure vigorous activity. Sedentary rats served as controls. Water temperature was strictly maintained between 33 and 35°C and at a depth of 55 cm. All swimming was continuous during specified periods and was closely monitored at all times by an experienced technician, who retrieved the rats at the moment of exhaustion. The end-point was arbitrarily taken as the time when the rat was submerged for approximately 10 sec, ceased all coordinated movements and could not return to the surface (13).

Experimental design. A series of four studies was performed to evaluate the influence of rat strain variation and previous swimming experience on performance capacity during the course of bacterial infections. In the first, 20 rats were studied per group. Naive rats were randomly selected from the general population, while experienced rats were selected by ability to complete a 60-min swim test (22) one week prior to the day of experiment. Animals unable to perform this test were discarded. Rats were subsequently inoculated with varying concentrations of either microorganism and then forced to swim to exhaustion on day 3 postinoculation.

In a separate study, 15 naive and experienced rats per dose were inoculated and immediately exhausted (12) or limited to 3-h period. The animals were then allowed to rest for the next 7 days and mortality was monitored. Based of these first two studies, all further experiments used experienced rats.

The third study was performed to determine whether there was a critical period prior to, or immediately following, inoculation, during which exercise would most likely influence disease-related mortality. All animals used had access to food throughout this study. Fifteen rats per group were injected with median lethal doses of either *S. pneumoniae* or *F. tularensis* at different intervals in relation to time of exercise. Rats were divided into four major groups and inoculated with LD_{50} doses of either organism at different intervals in relation to the exercise period: Group I rats were the sedentary-infected controls; Group II rats were exercised for 3 h immediately prior to inoculation

(Before); Group III rats were exercised for 3 h immediately following inoculation (After); and Group IV rats were exercised for 1.5 h immediately prior to and 1.5 h immediately after inoculation (Before and After). This procedure was utilized to insure work intensity and duration were equal among exercised groups.

The fourth series of studies was designed to ascertain the effect of repeated bouts of exercise (9) on successive days during two acute febrile infections. Only experienced animals were used. Designated infected rats were challenged with LD_{50} doses of either bacterium. The number of rats per group was varied to insure that 5 rats per group would survive the 72-h infection and repeated exercise. The same rats swam twice daily on days 0, 1 and 2 postinoculation. On day 3, these same animals and sedentary noninfected and infected rats were forced to swim to exhaustion.

Statistical tests. Two statistical tests were utilized to analyze results: the Fisher exact test to compare mortality data between infected and noninfected controls; and two-way analysis of variance (unpaired ANOV) to compare performance data between exercised and sedentary groups. $P \leq 0.01$ was considered significant in all studies.

RESULTS

Data on the dose-response and performance capacity relationships of sedentary-infected and exercised-infected rats are summarized in Figs. 1-5. Endurance was variable between the two strains of rats, which have been previously established as excellent animal models for infectious disease studies (2, 15-18, 25).

Swimming noninfected rats. Baker and Horvath (1) have outlined some of the swimming styles and patterns of normal rats. Our observations show similar characteristic behavior in both strains of rats studied, with a few exceptions. Initially, the rats thrash about, appear disoriented and attempt to escape. During this initial immersion, 40% of the naive Fisher and 4% of the naive Sprague rats require immediate removal because they appear to be drowning and have been labeled by Richter as exhibiting the "sudden death phenomenon" (20). Less than 10% of the Fisher and 1% of the Sprague rats die upon immediate retrieval from this phenomenon. Experience with the swimming task reduced these percentages. After the initial shock of water immersion, the remaining animals begin to pace themselves, conserving their energy and swimming in a circular motion, at a 45° angle to the surface. Bobbing and diving were present (12). As the animals reached final exhaustion, they tended to swim in the center of the barrel, twirled in a disoriented manner, and positioned themselves almost perpendicular to the surface. Submerged periods increased in number and duration (13).

Griffith and others (5,7 and 8) have reported maximum swimming times of 36 h for wild rats and 60 h for domestic rats in thermoneutral water. Our studies indicate that only 10% of the naive Fisher rats can swim for

6 h (median time of 3 h), while Sprague rats of the same sex, weight, and naivete averaged 3-fold longer swimming times (median time of 10 h).

Swimming infected rats. Infected rats exhibited similar swimming patterns and styles to noninfected animals, with two exceptions: increased ability to float and reduced performance capacity. The ability to float has been previously reported in healthy rats (1, 3, 13). Only 3% of the normal population of naive Fishers and 6% of the Spragues floated. These percentages increased with the amount of training the animal received. During infection these percentages also increased. More than 80% of the naive Fishers infected with 2.1×10^2 *S. pneumoniae* and 30% of the Spragues infected with 3.4×10^9 *F. tularensis* were positively buoyant at 72 h postinoculation, if they swam individually. Less than 20% and 3%, respectively, were buoyant when forced to swim in groups of five. Other investigators (3, 13) have proposed that this floating behavior is caused by trapped bubbles in the animals' fur. Our studies indicate they may be gulping air and storing it in their stomachs. Both of these behaviors may be adaptations to hyperthermia. Correlative studies show a rectal to water temperature difference of + 5.7°C in the swimming-infected rat compared to a + 3.5°C difference in exercised-noninfected rats. Larger abscesses at the injection site may contribute to the animals' buoyancy. It was found that infected rats' specific gravity was less than noninfected controls (volume of water displaced divided by the rats weight).

Figure 1 summarizes the influence of rat strain variations and experience on performance during model bacterial infections. Prior experience appeared to be beneficial (3, 13). It reduced individual rat variability and increased swimming performance times in both strains, with greater effects observed in Fisher-Dunning rats. The apparently high natural resistance of Sprague-Dawley rats to both microorganisms has been well-documented (17) and is supported by our studies. Sprague-Dawley rats exhibited some significant differences ($\underline{P} < 0.05$) in performance between experienced and naive animals (Fig. 1). The percent reduction in swimming time increased with the size of the inocula. Pneumococcal sepsis in Fisher rats reduced performance proportionally (48% for 2.1×10^1 and 83% for 2.1×10^2 doses). Although these trends were present in tularemic rats, the magnitude of the reduced performance was only observed at higher concentrations (30% for 3.2×10^6 and 75% for 3.2×10^7 doses). It was also observed that a greater proportion of naive rats were unable to swim at 72 h postinoculation with LD_{50} doses of the model diseases.

Mortality due to S. pneumoniae and F. tularensis in sedentary-infected and exercised-infected naive and experienced rats is presented in Fig. 2. We have established that the 72-h median lethal dose for these diseases is 2.1×10^2 and 3.2×10^6, respectively, for the Fisher rats: the LD_{50} of these infections are a log higher for Sprague-Dawley rats. Values may change based on several variables (15, 18). In this dose-response study, data suggest that both bacterial infections show higher mortality rates for exercised-infected animals. This is supported by the lower LD_{50} dose for swimming-infected rats compared to their sedentary controls. Strenuous exercise reduced the LD_{50} for pneumonia and tularemia in Fisher rats to less than 2.1×10^1 and 3.2×10^5, respectively, and a log higher dilution of both diseases in Sprague-Dawley rats. While swimming did not increase mortality at sublethal doses of S. pneumoniae, it showed an effect with sublethal concentrations of F. tularensis.

Results (Fig. 3) suggest that a 3-h swim immediately before inoculation drastically reduced disease-related deaths in both strains for the diseases studied. Similar patterns were observed in all other treatments with a trend in the exercised animals to have a slightly higher mortality compared to sedentary controls. The swimming after inoculation appears to have the most severe effect on death rate and cancels the beneficial influence of preinoculation swimming.

Experienced rats infected with LD_{50} doses of either bacterium and forced to swim 2 h daily during the course of the infections, showed altered mortality over the 3-day period (Fig. 4). The survival of infected rats was significantly decreased by daily exercise after inoculation. Only 10% of the pneumococcal infected-exercised Fisher rats were alive on day 3 compared to 30% survival in the infected-sedentary group. Similar trends were also apparent in both strains during tularemia infection, but were less pronounced in Sprague-Dawley rats.

Data indicate (Fig. 5) that when experienced rats are exercised to exhaustion on day 3 after a LD_{50} challenge of either bacterium, each strain of rat becomes exhausted rapidly. The maximum swimming times were reduced by 96% in pneumococcal and 90% in tularemia infected sedentary Fisher rats. While a slight improvement in the time to exhaustion was observed in the infected rats surviving the daily sessions of exercise, results show an 84 and 85% reduction in performance capacity associated with pneumococcemia and tularemia, respectively. However, daily exercised rats showed a greater than 12% improvement over the sedentary-infected controls. In contrast, the point of exhaustion in Sprague rats was reduced only 61% in the pneumococcal and 66% in the tularemic sedentary-infected animals.

These rats demonstrated similar trends to Fisher rats and showed an even greater improvement (20%) due to daily exercise, a characteristic of training regimens (9).

DISCUSSION

In order to evaluate alterations in performance capacity a usable model had to be developed. Swimming was chosen as a reliable means of exercising rats (3, 13) and S. pneumoniae (15) and F. tularensis (18) as representative bacterial infections. Results demonstrated rat strain differences in response to infection and exercise, which necessitated a standarization of work performance. Studies also indicated that either microorganism caused decrements in performance and that the time of exercise in relation to organism inoculation time was important; exercise postinoculation increased disease lethality, while a swim preinoculation reduced susceptibility.

Changes in working capacity may be related to the animals' instinctive behavior. These aspects have been reviewed (9, 24). Kimeldorf has defined performance as behavior in a particular environment (9). He pointed out that in creating a situation for evaluation of performance, one must insure that all subjects behave consistently during the situation. Our studies have attempted to reduce behavioral variability to a minimum. A 60-min exposure to the swimming task seemed to reduce large variations in individual performance times of both strains of rats. McArdle and Montoye (13) suggested that this prior experience serves two important purposes. It reduces learning factors and improves reliability of the measured task significantly above pretrained level. The proper strain selection is therefore essential, since rats vary in intelligence, stamina and adaptability (8).

Experience seemed to reduce sudden death, while infection increased the occurrence. The reasons for this phenomenon are unclear. Richter (20) suggested a respiratory or vascular reaction to immersion. He believed that this is a hopeless response caused by overactivity of the parasympathetic system. Other evidence suggested that the greater susceptibility to this phenomenon in wild rats indicated a higher vagal tone (20), and specifically in the dorsal motor nucleus of the vagus. Recent results suggest cardiovascular failure as being responsible for the phenomenon, with primary emphasis on the cardiac muscles themselves. Coxsackie B-3 myocarditis has been reported to cause congestive heart failure during swimming. This was probably due to increased replication of viruses in the myocardium (11, 19). But no pathologic lesions compatible with myocarditis were detected in the hearts of animals exhibiting this syndrome when infected with *S. pneumoniae* or *F. tularensis* (personal observation). The lack of cardiac muscle pathology in these infected rats is supported by the work of Moe et al. (14) and suggests that sudden cardiac arrest as shown by Richter (20) is due to a neurologic or biochemical process rather than a pathologic one.

In fact, the infectioninduced decrement in performance has been related to physiologic and biochemical alterations (22, 23). Studies by Friman et al. (6) involving localization of the infectious process in the heart and skeletal muscle of infected rats have indicated changes in the protein synthesis mechanisms and enzyme activity. Our preliminary studies indicate that exercise superimposed on bacterial infection does not alter the direction, but does alter the magnitude of energy substrate utilization (manuscript in preparation).

Swimming exercise influences disease lethality (Fig. 2-4). The mechanisms by which fatigue may increase susceptibility to bacterial infections is not known. However, the possibility exists that exercise affects the adrenal cortex causing increases or decreases in hormonal secretion, which in turn effects increased reticuloendothelial clearance of the microorganism.

The effects of exercise on disease lethality also vary with the relative time of disease exposure. Results (Fig. 3) indicate that postinoculation exercise induced an increase, while preinoculation exercise reduced disease-related mortality. Although fever (data not shown) was observed in the preinoculation exercised group, the response was less pronounced than sedentary-infected and postinoculation exercised groups. The studies of Postel *et al.* (17) proposed that moderate early swimming was beneficial and late swimming was deleterious to diphosgene-gassed animals. This coupled with the fact that less than exhaustive exercise of significant duration immediately prior to the disease inoculation is beneficial, suggests that exercise stimulates protective mechanisms.

Repeated sessions of exercise following inoculation increased the disease-related mortality (Fig. 4). Other investigators (10, 11, 17, 19) have obtained similar results using various pathologic conditions. A training response (3, 21) was observed in the time to exhaustion in infected animals forced to swim daily during the infection (Fig. 5). Previous studies (6) suggested that swimming capacity, although reduced by an infection, was slightly altered by daily exercise during the acute phase of the illness. The effects of training and prior experience on performance are not entirely clear, but it appears that swimming is less severe both in terms of performance and disease mortality for daily exercised rats, because they have learned to eliminate wasted motion. The amount of experience begins to play an important role in the improved performance capacity of septic animals, even during the stress of the infection. Data suggest that exercise during the course of infection increased mortality. However, those animals which survived for 72 h had been trained by daily exercise, so that the decreases in performance were reduced. One presumes that this might represent a special condition related to the selected animals which survived the infection and not the infected population as a whole.

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FIGURE LEGENDS

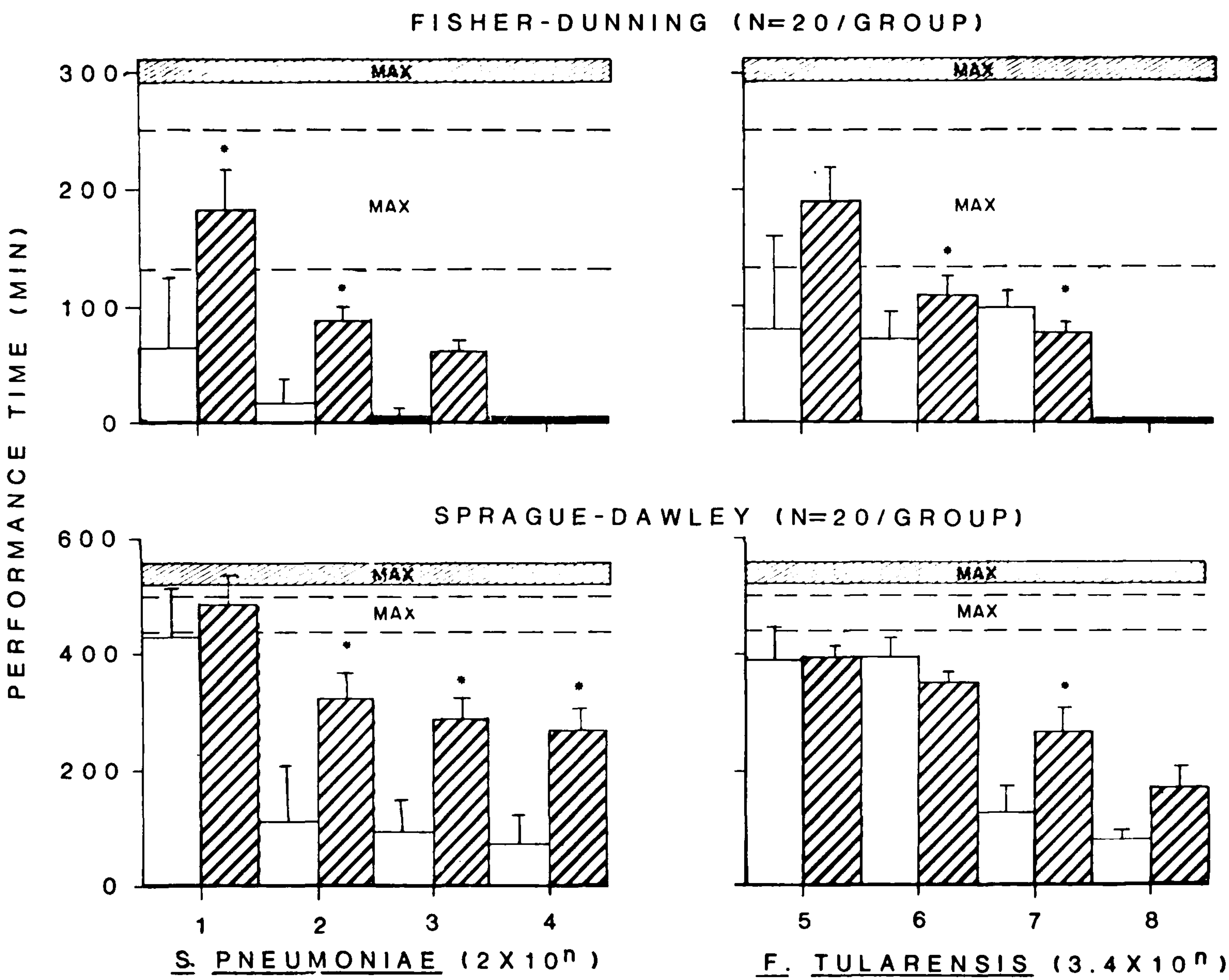
Fig. 1. Influence of S. pneumoniae and F. tularensis on swimming performance capacity of naive and experienced rats. "Experienced" rats were subjected to a 60-min swim 1 week prior to inoculation. Horizontal bars represent the maximum swimming time of both naive and experienced rats. (n = log dilution of bacteria on abscissa). Each bar represents the mean $\pm$ S.E.M. for 20 rats. $^{*}P < 0.01$ ANOVA (unpaired) between naive exercised and experienced-exercised groups.

Fig. 2. Effect of a 3-h swim on survival of experienced rats infected with varying doses of either bacterium. Abscissa indicates dose. Each bar represents the percent survival of 15 rats 72 h after inoculation. $^{*}P < 0.01$ using ANOVA (unpaired) between naive and experienced groups.

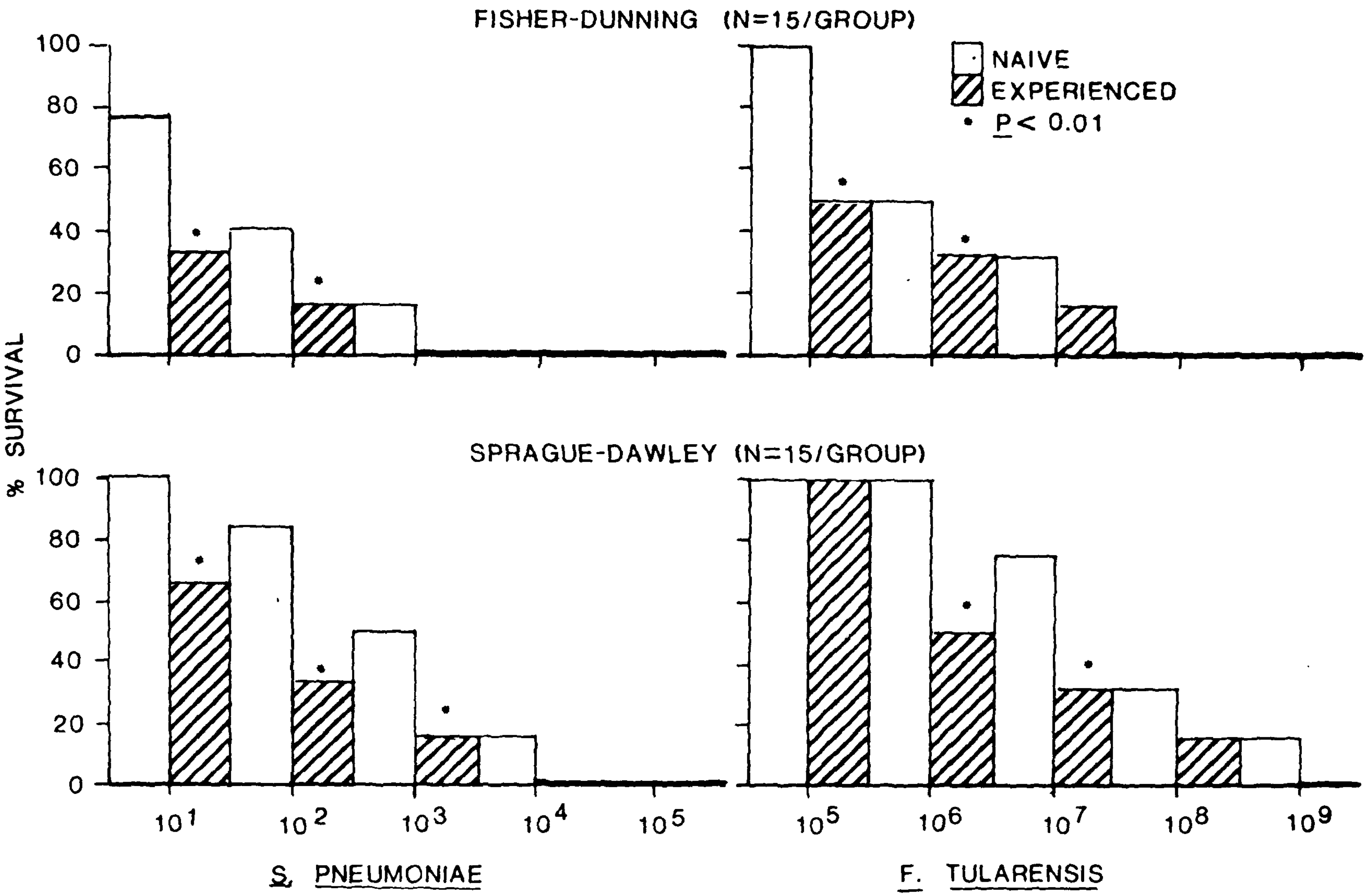
Fig. 3. Influence of a 3-h swim at various times relative to infection with LD_{50} doses of S. pneumoniae and F. tularensis on survival of experienced rats. "Before" groups swam 3 h prior to inoculation. "After" groups swam 3 h immediately following inoculation. "Before and After" groups swam 1.5 h before inoculation and 1.5 h after. Lines represent groups of 15 rats at different time intervals. Animals were fed throughout the study. $^{*}P < 0.01$ using ANOVA (unpaired) between sedentary and exercised groups 3 days postinoculation.

Fig. 4. Detrimental effect of daily swimming exercise on percent survival of experienced rats during the course of LD_{50} challenge with either microorganism. Following inoculation, animals were forced to swim for 2 h twice daily for 3 days. $^{*}\underline{P} < 0.01$ using Fisher's exact test between infected and noninfected groups.

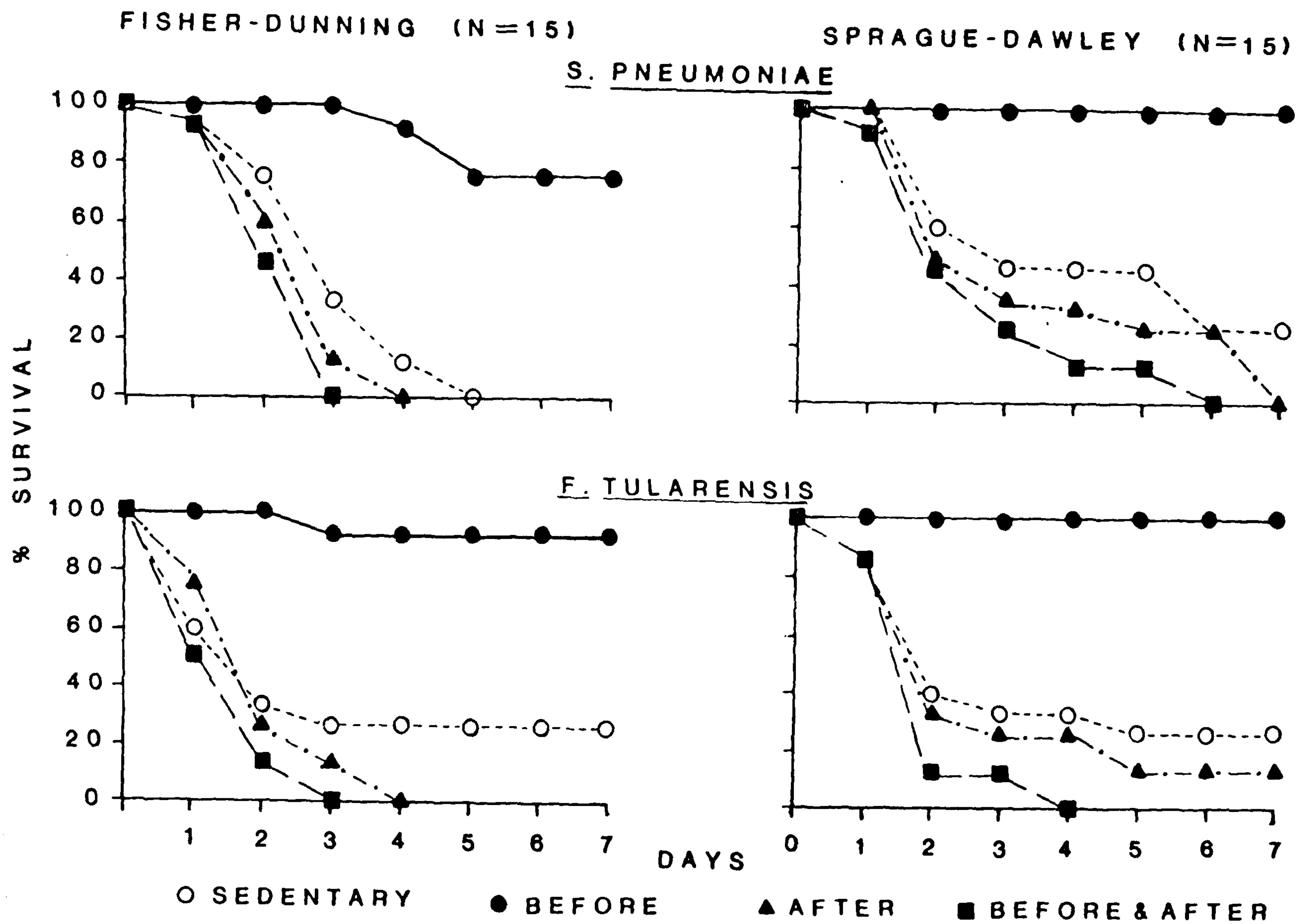
Fig. 5. Time to exhaustion of experienced rats exercised daily during the course of LD_{50} infection with either disease. $^{*}\underline{P} < 0.01$ using Fisher's exact test between infected and noninfected groups.



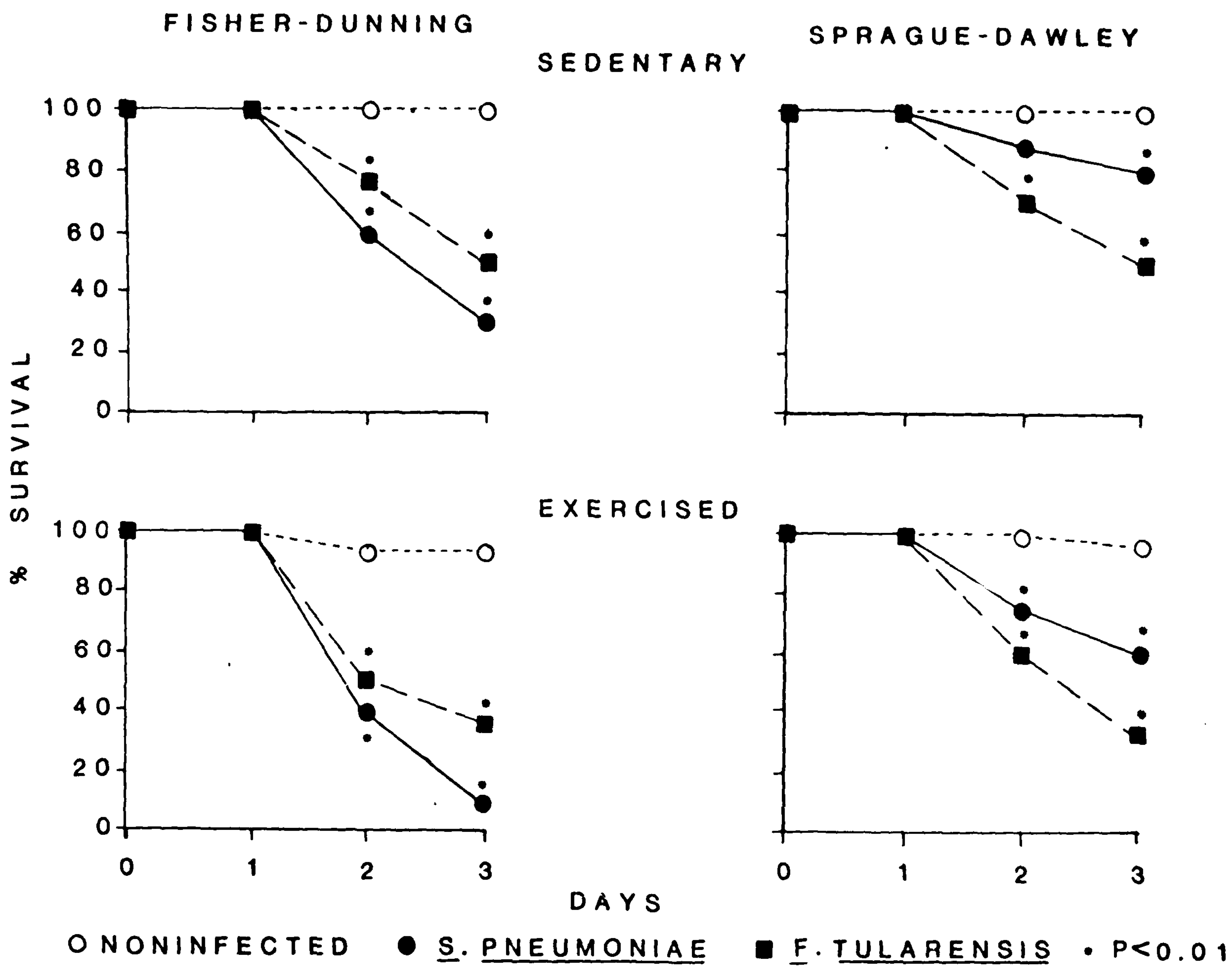
FISHER-DUNNING (N=20/GROUP)
SPRAGUE-DAWLEY (N=20/GROUP)
PERFORMANCE TIME (MIN)
MAX
0
100
200
300
400
600
1
2
3
4
5
6
7
8
S. PNEUMONIAE (2X10ⁿ)
F. TULARENSIS (3.4X10ⁿ)



FISHER-DUNNING (N=15/GROUP)
NAIVE
EXPERIENCED
• P< 0.01
% SURVIVAL
100
80
60
40
20
0
SPRAGUE-DAWLEY (N=15/GROUP)
10^1
10^2
10^3
10^4
10^5
10^5
10^6
10^7
10^8
10^9
S. PNEUMONIAE
F. TULARENSIS



FISHER-DUNNING (N=15)
SPRAGUE-DAWLEY (N=15)
S. PNEUMONIAE
F. TULARENSIS
% SURVIVAL
100
80
60
40
20
0
DAYS
0 1 2 3 4 5 6 7
○ SEDENTARY
● BEFORE
▲ AFTER
■ BEFORE & AFTER



FISHER-DUNNING
SPRAGUE-DAWLEY
SEDENTARY
EXERCISED
% SURVIVAL
100
80
60
40
20
0
0
1
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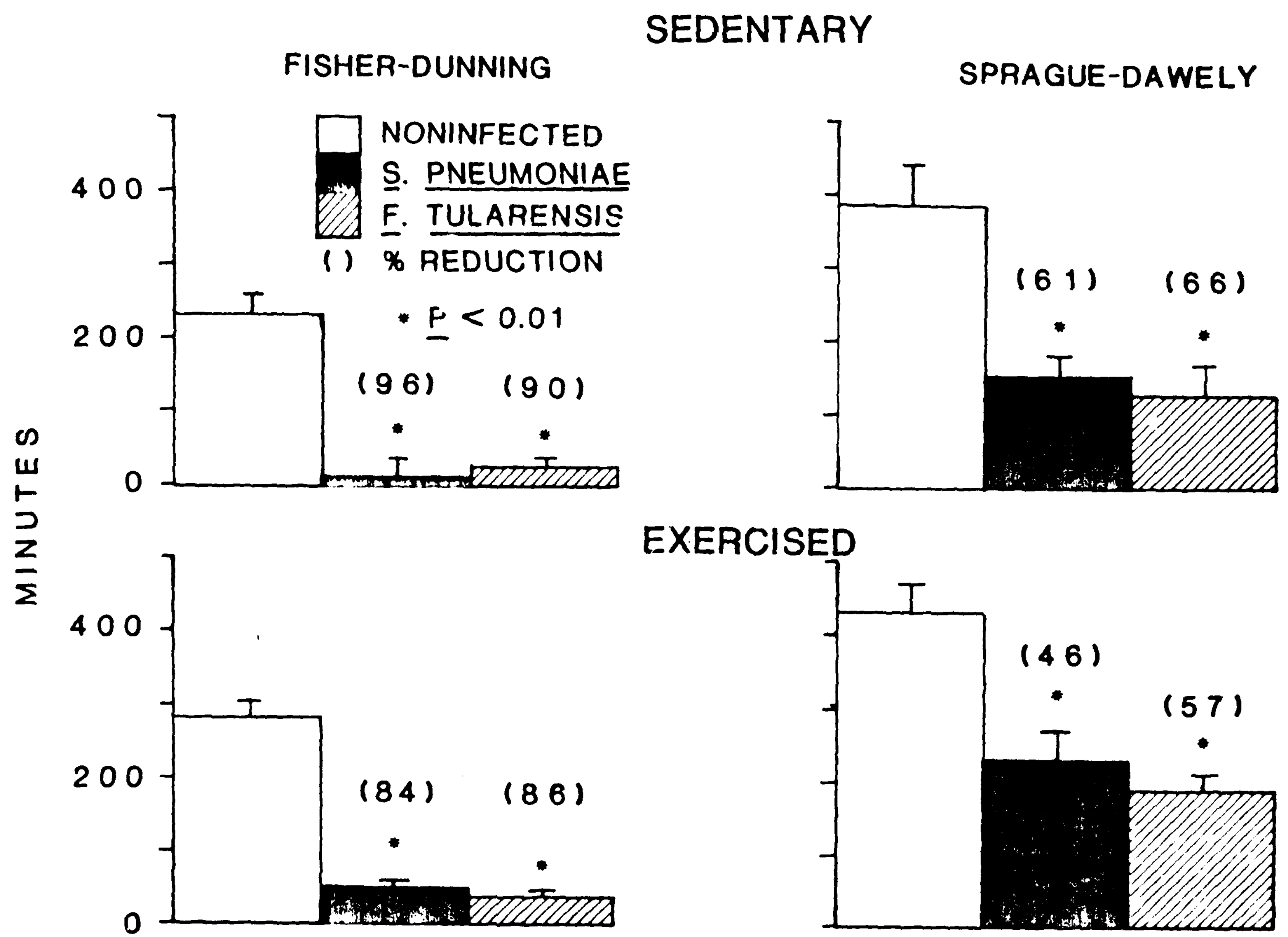
DAYS
O NONINFECTED
● S. PNEUMONIAE
■ F. TULARENSIS
• P<0.01



SEDENTARY
FISHER-DUNNING
SPRAGUE-DAWELY
NONINFECTED
S. PNEUMONIAE
F. TULARENSIS
( ) % REDUCTION
* P < 0.01
MINUTES
400
200
0
(96)
(90)
(61)
(66)
EXERCISED
(84)
(86)
(46)
(57)

DATE
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